Nebulizing and drug delivery device

Field of the Invention

The present invention relates broadly to a nebulizer, and in particular an ultrasonic nebulizer, as well as a method and a device for delivering a substance in an aerosol form into a cellular organism. The invention also relates generally to a handheld device for delivering a substance to a cellular organism. The invention relates particularly, though not exclusively, to nebulization of drugs and radiation or energy assisted delivery of aerosol and non aerosol forms of drugs to cellular organisms.

Background to the Invention

Drugs are commonly administered orally by absorption through a patient's digestive tract or intravenously via syringes or drips, directly into a patient's veins. Both of these methods of drug administration involve systemic delivery of high doses of a drug which results in only a small percentage of the drug reaching a target area. Because of the high dosage, toxic side effects are often involved. In order, to address these problems alternative forms of drug delivery are being used for an increasing number of applications. The alternative forms of drug delivery typically involve: (i) inhalation, and (ii) trans skin or transdermal transport which is technically known as transdermal drug delivery.

Drug delivery via inhalation can involve an aerosol form of a drug. Aerosol forms of a drug are usually provided by atomization of a liquid solution form of the drug to form aerosol, immediately prior to drug delivery. Atomization is typically most efficiently effected by nebulization of a liquid, usually but not exclusively, with an ultrasonic nebulizer.

Ultrasonic nebulizers typically include an ultrasonic transducer which is positioned below a liquid filled container. For example, in more efficient nebulizers the ultrasonic transducer is designed to focus ultrasonic radiation to a specific point within the container. The focussed radiation results in formation of an upwardly projecting fountain of liquid and the formation of aerosol droplets at the fountain. Ultrasonic nebulizers operate efficiently when the liquid surface passes through the focal point of the ultrasonic transducer. However, they operate poorly or not at all if the liquid surface is above or

below the ultrasonic transducer focal point. Conversion of liquid to aerosol causes the liquid surface to lower which in turn adversely affects a nebulizer's efficiency.

Transdermal drug delivery can involve passive diffusion and active transport. Passive diffusion of a drug through the skin is the diffusion that occurs naturally when small-molecule drugs are applied to the skin in sufficient concentration and for a sufficient period of time to enable natural diffusion through the skin. However, passive diffusion is slow and furthermore, because of the skin's natural barriers to passage of externally applied substances, passive diffusion is not suitable for most drugs. Active transdermal drug delivery techniques include sonophoresis, iontophoresis, electroporation and magnetophoresis. Sonophoresis involves the application of ultrasound, iontophoresis and electroporation involve the application of an electric field and magnetophoresis involves the application of a magnetic field.

US patent 5741317 discloses an apparatus which includes a therapy and drug treatment tub for submersion of a treatment area of a patient in a medicated solution. The tub includes acoustic transducers and rows of electrodes and coils for delivery of respective ultrasonic, electric and magnetic radiation to the patient. The radiation facilitates active transdermal drug delivery involving phonophoretic, iontophoretic and electromagnetophoretic transport mechanisms. However, the apparatus is very large and expensive and cannot readily be used for transdermal drug delivery to a specific region of a patient.

US patent 5983134 discloses a flexible cuff connected to a liquid drug reservoir. The cuff is designed for attachment to a patient by wrapping around part of the patient's body to form an attached sleeve. Referring to figure 1 of US 5983134, the attached sleeve can be elongate and encircle most of a patient's leg, or squat and encircles a patient's neck. The cuff is designed to transmit electric and magnetic fields to assist transdermal delivery of drugs provided at an internal cylindrical surface of the attached sleeve. While the cuff of US 5983134 is suitable for transdermal drug delivery to a specific part of a patient's body, it is cumbersome to use and is only suitable for delivery of a drug to a circumferential segment of a patient's limb, torso or neck.

US patent 5464386 discloses a transdermal drug delivery applicator which is designed to supply a fluid medium carrying drug loaded vesicles to a patient's skin via a

curved head assembly. The applicator generates a pulsed electrical field to facilitate active transdermal transport mechanisms of electroporation and iontophoresis. The applicator is capable of providing active transdermal drug delivery to a specific part of a patient's body. However, the applicator is only able to provide active transdermal drug delivery involving electric radiation.

Summary of the Invention

According to one aspect of the present invention there is provided a method of delivering a substance into a cellular organism, the method comprising the steps of:

providing the substance in an ionised aerosol form at a delivery region of the organism; and

applying magnetic energy to the delivery region to effect enhanced delivery of the ionised aerosol substance to the cellular organism.

Preferably the application of magnetic energy is effected by applying a pulsed magnetic field. More preferably the pulse magnetic field is asymmetric.

According to another aspect of the invention there is provided a method of delivering a substance into a cellular organism, the method comprising the steps of:

providing the substance in a liquid or cream form at a delivery region of the organism;

applying ultrasonic energy to the delivery region to enhance delivery of the cream or liquid substance to said organism; and

simultaneously applying magnetic energy and electrical energy to the delivery region to effect delivery of the cream or liquid substance to the cellular organism.

Preferably the application of ultrasonic energy to said organism to enhance delivery is promoted by opening of pores of the organism.

Preferably the ultrasonic and magnetic energies are applied simultaneously.

Preferably the application of ultrasonic, magnetic and/or electrical energy is effected by applying ultrasonic, magnetic and/or electrical fields, respectively, the magnetic field is a pulsed magnetic field.

According to a further aspect of the invention there is provided a device for delivering a substance into a cellular organism, the device comprising:

an aerosol delivery head for providing the substance in an ionised aerosol form at a delivery region of the organism;

means for applying magnetic energy to the delivery region to effect enhanced delivery of the ionised aerosol substance to the cellular organism.

Preferably the aerosol delivery head is configured to defines a sealed compartment about the delivery region.

Preferably the device also comprises a nebulizer being operatively coupled to the aerosol delivery head. More preferably the nebulizer includes:

a container being adapted to contain a liquid to be nebulized;

a tubular energy transmitter having one end immersed in the liquid of the container and an opposite end positioned clear of the liquid; and

an energy source being operatively coupled to the container or the tubular energy transmitter for nebulization of the liquid and being arranged for transmission of energy to the liquid or tubular energy transmitter whereby in operation the transmitted energy forces the liquid toward the opposite end of the tubular energy transmitter where it is nebulized in the form of the aerosol.

Preferably the energy transmitter is positioned so that said one end is adjacent the bottom of the liquid.

Preferably the energy transmitter is arranged to allow formation of high frequency vibrations in its wall(s) upon emission of the energy, the high frequency vibrations effecting aerosol formation at the liquid surface at or adjacent the opposite end of the energy transmitter.

Preferably the nebulizer also includes an aerosol tube coupled to the opposite end of the tubular energy transmitter and having a cross-sectional area such that the static pressure of the aerosol within the aerosol tube induces a pressure drop along the aerosol tube which alone is sufficient to propel the nebulised aerosol through the aerosol tube.

According to yet another aspect of the invention there is provided a device for delivering a substance into a cellular organism, the device comprising:

means for generating ultrasonic energy being adapted to cooperate with a delivery region of the organism to enhance delivery of the substance in a cream or liquid form to said organism;

means for simultaneously applying magnetic energy and electrical energy to the delivery region to effect delivery of the cream or liquid substance to the cellular organism, said ultrasonic generating means being operatively coupled to the magnetic and electrical energy means whereby a synergistic effect is provided by the combination of said means.

Preferably the means for applying magnetic energy is in the form of a pulsed magnetic generator.

The organism of the various aspects of the present invention may be an animal. More particularly, the organism may be a human being. The delivery region may comprise a membrane of the animal or human being. The membrane may comprise skin of the human being. Alternatively, the membrane may comprise a cornea of the human being. The membrane may alternatively comprise a lung of the human being.

Brief Description of the Drawings

A preferred embodiment of the present invention will now be described, by way of example only, with reference to the accompanying drawings, in which:

Figure 1 is a schematic side elevational view of part of an ultrasonic nebulizer disclosed in the applicant's US patent;

Figure 2 is a schematic side elevational view of part of one example of an ultrasonic nebulizer of the present invention which has an ultrasonic transducer positioned beneath liquid which is contained in the nebulizer;

Figure 3 is a schematic side elevational view of part of another example of a nebulizer of the present invention having an ultrasonic transducer positioned above liquid contained in the ultrasonic nebulizer;

Figure 4 is a schematic side elevational view of a third example of an ultrasonic nebulizer of the present invention;

Figure 5 is a schematic side elevational view of a magnetic radiation transdermal aerosol delivery gun;

Figure 6 is a schematic side elevational view of one example of internal components of a substance delivery gun similar to the aerosol delivery gun of figure 5;

Figure 7 is a fluorescence confocal image of a stratum corneum skin layer showing active transdermal delivery of a fluorescent dye to this layer of a subject using the substance delivery gun of figure 6;

Figure 8 is an image corresponding to that of figure 7 of a deeper skin layer, the stratum spinosum;

Figure 9 is an image corresponding to that of figure 7 showing slightly deeper penetration of the fluorescent dye;

Figure 10 is a schematic side elevational view similar to that of figure 6 showing another example of internal components of the substance delivery gun of figure 6; and

Figure 11 is a schematic side elevational view similar to that of figure 6 showing a third example of internal components of the substance delivery gun of figure 6.

Detailed Description of the Preferred Embodiment

US patent No. 5908158 discloses the applicant's ultrasonic nebulizers which are predecessors to the preferred form of nebulizer of the present invention. The contents of US 5908158 are hereby incorporated into this specification. Figure 1 is a schematic representation of the nebulizer of US 5908158. The nebulizer 10 includes a container in the form of bowl shaped container 12 which contains liquid 14, an energy source in the form of bowl shaped ultrasonic transducer 16 and an aerosol tube 18. The bowl shaped ultrasonic transducer 16 is designed to focus emitted ultrasonic radiation energy at an acoustic focal region, in this example acoustic focal point 20, which is located just beneath an upper surface of the liquid 14. Energy absorbed at the acoustic focal point 20 by the liquid 14 causes liquid to project upwardly to form a liquid spout 22.

In addition to formation of the liquid spout 22, ultrasonic radiation focussed at the acoustic focal point 20 results in transmission of acoustic energy upwardly through the liquid spout 22. When the acoustic energy reaches an upper surface 24 of the liquid spout 22 it results in nebulization of liquid molecules which form at the upper surface 24 and the subsequent formation of aerosol 26. Aerosol formation is understood to occur by a process which most likely involves capillary wave and cavitation mechanisms involving high frequency vibrations.

The liquid 14 can be a liquid or liquid suspension form of any substance which is required in an aerosol form. For example, the liquid 14 could include a medicated substance, for example a drug, or alternatively could be a perfume. The aerosol 26 is a vaporised form of the liquid 14 and can be administered to a cellular organism which for the purpose of this example is a person or patient. The aerosol 26 can be administered to a patient, for example, by inhalation or transferral through external cells of a patient's body such as those comprising their skin or cornea.

The aerosol 26 is administered to a patient by propelling it upwardly through the aerosol tube 18 which corresponds to the intake tube of the applicant's US patent No. 5908158. Aerosol 26 formed from the nebulizer can be administered to a patient by placing a delivery region, which in this example is a patient treatment site or specific part of a

patient's body, near the aerosol 26 and allowing the aerosol 26 to be administered to the patient treatment site by diffusion.

As the liquid 14 is nebulized by the nebulizer 10 and aerosol 26 is formed above the liquid 14, this nebulization of the substance results in depletion of the volume of liquid 14 which is contained by the bowl shaped container 12. As the volume of liquid 14 decreases the upper surface 15 of the liquid 14 moves downwardly. Once the upper surface 15 moves below the acoustic focal point 20 the rate of conversion of liquid 14 to aerosol 26 dramatically reduces to cause a corresponding reduction in efficiency of operation of the nebulizer 10.

Figure 2 shows one example of an ultrasonic nebulizer 30 of the present invention. For ease of reference like features of this ultrasonic nebulizer 30 and the previously described nebulizer 10 are referenced by common reference numerals. The ultrasonic nebulizer 30 includes a bowl shaped container 12 which contains liquid 14 having an upper surface 15, a bowl shaped ultrasonic transducer 16 and an aerosol tube 18. The ultrasonic nebulizer 30 also includes ultrasonic transmission media in the form of water which is positioned between the bowl shaped ultrasonic transducer 16 and the bottom of the bowl shaped container 12. The nebulizer 30 also includes a tubular energy transmitter in the form of an acoustic transmitter pipe 34 which is supported by the aerosol tube 18 via a connection plate which in this example is an annular disc 36. The acoustic transmitter pipe 34 is cylindrical in shape however the tubular energy transmitter is not limited to this shape. For example, in an alternative form the tubular energy transmitter is a bell-shaped pipe (not shown). The transmitter pipe 34 and the aerosol tube 18 are arranged coaxial with one another. The annular disc 36 includes connection plate apertures in the form of holes 38. The bowl shaped ultrasonic transducer 16 focuses ultrasonic radiation at acoustic focal point 40 which is just above the bottom of the liquid 14 but below one end of the acoustic transmitter pipe 34 which in this particular example is a lower end 42. The correct focal point is achieved by appropriately designing the radius of curvature of the bowl shaped ultrasonic transducer 16 and the spacing between it and a bottom of the bowl shaped container 12.

Absorption of ultrasonic radiation energy by liquid 14 at the acoustic focal point 40 forces water upwardly through the acoustic transmitter pipe 34 to form a guided liquid spout 44. The guided liquid spout 44 extends beyond an upper surface of the acoustic

transmitter pipe 34 and the annular disc 36 as shown in figure 2. Energy imparted to the liquid 14 at the acoustic focal point 40 results in transmission of acoustic energy upwardly through the guided liquid spout 44 and the wall of the acoustic transmitter pipe 34 The acoustic energy also transmits to the annular disc 36. The presence of acoustic energy at an upper surface 46 of the acoustic transmitter pipe 34, upper surface 48 of the annular disc 36 and upper longitudinal and lateral surfaces 50 and 52 respectively of the guided liquid spout 44, result in the formation of aerosol at those surfaces. In addition to supporting the acoustic transmitter pipe 34 the annular disc 36 increases the rate of which liquid 14 is converted to aerosol 26. Delivery of aerosol 26 formed by the ultrasonic nebulizer 30 to a patient treatment site (not shown) is as explained above in relation to the nebulizer 10.The acoustic impedance of the acoustic transmitter pipe 34 is higher than that of the liquid 14 to prevent radiation dispersing from the acoustic transmitter pipe 34 during transmittal along it. The acoustic impedance is high enough to effect minimal acoustic energy loss during transmission of the ultrasonic radiation.

Figure 3 shows an example of a radially spaced energy source in the form of an ultrasonic transducer 56 which encircles a longitudinal mid segment 58 of a tubular energy transmitter in the form of an acoustic transmitter pipe 60. The ultrasonic transducer 56 and acoustic transmitter pipe 60 can be substituted for the ultrasonic transducer 16, ultrasonic transmission media 43 and acoustic transmitter pipe 34 of the ultrasonic nebulizer 30 to form ultrasonic nebulizer 54. The ultrasonic transducer 56 transmits ultrasonic radiation energy directly to the acoustic transmitter pipe 60 and the liquid 14. Ultrasonic radiation energy absorbed by the liquid 14 results in the liquid14 being forced upwardly through the acoustic transmitter pipe 60 to form a guided liquid spout 44. The mechanism which is understood to be responsible for formation of the guided liquid spout 44 is known as the sonocapillary effect. Energy imparted to the acoustic transmitter pipe 60 is transmitted upwardly along walls of the acoustic transmitter pipe 60 as explained above in relation to the acoustic transmitter pipe 34. Liquid is nebulized as explained above in relation to the ultrasonic nebulizer 30 by interaction of the acoustic energy with the liquid spout and upper surfaces of the acoustic transmitter pipe 60.

The ultrasonic nebulizers 30 and 54 can include additional components described in relation to the ultrasonic nebulizer of US patent No. 5908158. For example, the ultrasonic nebulizers 30 and 54 can include an expansion chamber, for example, expansion chamber 9 of nebulizers of US 5908158 (see figures 1, 2, 3, 4, 6 and 8) and an outlet duct. Examples of

outlet ducts are ducts 11, 26 and 29 of figures 1, 5 and 6 of US 5908158. In ultrasonic nebulizers 30 and 54 which include an expansion chamber (not shown), the aerosol tube 18 functions as the intake tube 8 of US patent 5908158 and can be supported relative to an expansion chamber in a similar manner to that which the intake tube 8 of US 5908158 is supported relative to expansion chamber 9. An expansion chamber enables any un-nebulize drops of liquid which issue from the aerosol tube 18 to be recirculated back into the liquid 14 as described in US 5908158, for subsequent nebulization. Ultrasonic nebulizers 30 and 54 which include an expansion chamber and an aerosol tube 18 which is free of the acoustic transmitter pipe 34 or 60 respectively, still include a flange at upper ends 35 and 61 of acoustic transmitter pipes 34 and 60 respectively which in this example corresponds to annular discs of 36 and 70 respectively.

The cross sectional area of the aerosol tube 18 of ultrasonic nebulizers 30 and 54 referred to above is such that the static pressure of aerosol 26 within the aerosol tube 18 induces a pressure drop as aerosol 26 moves upwardly along the aerosol tube 18. This pressure drop propels aerosol 26 upwardly through the aerosol tube 18 avoiding the need for any independent means of propulsion, eg a fan. Correct cross sectional dimensions of the aerosol tube 18 ensure that aerosol 26 can be efficiently and effectively admitted to a patient treatment site (not shown).

Referring to figure 4, an ultrasonic nebulizer 80 is described using reference numerals of the nebulizer 10 of figure 1 and ultrasonic nebulizers 30 and 54 of figures 2 and 3, respectively, to describe common features. The ultrasonic nebulizer 80 includes a bowl shaped container 12 which contains liquid 14, a bowl shaped ultrasonic transducer 16, ultrasonic transmission media 32 for transmission of ultrasonic radiation emitted by the bowl shaped ultrasonic transducer 16 to the liquid 14. The ultrasonic nebulizer 80 also includes an acoustic transmitter pipe 82 which is similar to the acoustic transmitter pipe 34 of the ultrasonic nebulizer 30. The acoustic transmitter pipe 82 is supported relative to the bowl shaped container 12 by an annular support disc 84 which sits on top of the bowl shaped container 12 to enclose the container 12. Ultrasonic radiation emitted by the bowl shaped ultrasonic transducer 16 is focused to an acoustic focal point 40 as described above in relation to the ultrasonic nebulizer 30. Aerosol 26 is formed at an upper end 86 of the acoustic transmitter pipe 82 also as described above in relation to the ultrasonic nebulizer 30.

The ultrasonic nebulizer 80 differs from examples of ultrasonic nebulizers 30 and 54 described above in that it includes an expansion chamber which in this example is expansion chamber 86. Expansion chamber 86 includes an outlet duct in the form of outlet pipe 88. The outlet pipe 88 is partitioned from the acoustic transmitter pipe 82 by an upright partition wall 90 which is positioned to one side of the expansion chamber 86 to form a main compartment 92 which is positioned directly over the acoustic transmitter pipe 82 so that the acoustic transmitter pipe 82 is approximately aligned with an upright longitudinal axis of the main compartment 92. The partitioned wall 90 also forms a side compartment 94 which connects to a side compartment drain pipe 96 that extends downwardly through a hole 98 in the annular support disc 84 and into the liquid 14 of the bowl shaped container 12. The expansion chamber 86 is supported relative to the bowl shaped container 12 by the annular support disc 84. The partition wall 90 stops short of an upper inner surface of the expansion chamber 86 for movement of gas between the main and side compartments 92 and 94 respectively.

The cross sectional area of the main compartment 92 is such that aerosol 26 which is formed at the upper end 87 of the acoustic transmitter pipe 82 is propelled upwardly within the main compartment 92 by the static pressure drop referred to above in relation to nebulizers 30 and 54. When aerosol 26 moving upwardly within the main compartment 92 meets an upper inner surface of the expansion chamber 86 it is directed by that surface to flow over an upper end of the partition wall 90 and into an upper end of the side compartment 94. Because of the propulsion provided to the aerosol 26 as it moves upwardly within the main compartment 92, the aerosol 26 is forced downwardly into the side compartment 94. As the aerosol 26 flows in a downward direction it passes the outlet pipe 88 which provides a lower energy route than if the aerosol 26 were to continue downwardly beyond the outlet pipe 88. The aerosol 26 therefore exits the side compartment 94 via the outlet pipe 88 for administration to a patient treatment site (not shown).

Liquid 98 in the main compartment 92 and side compartment 94 can occur either by liquid being projected directly upwardly from the acoustic transmitter pipe 82 by virtue of ultrasonic energy applied to the liquid 14 at the acoustic focal point 40 or by condensation of aerosol 26 during circulation of aerosol 26 from the main compartment 92 to the side compartment 94. When the ultrasonic nebulizer 80 is optimally adjusted the liquid 98 includes a minimal un-nebulized component and therefore effectively only comprises

condensed aerosol 26. Most of the condensed aerosol 26 circulates into the side compartment 94 for drainage down into the liquid 14 via the side compartment drain pipe 96.

Referring to figure 5, aerosol produced by the ultrasonic nebulizers 30, 54 and 80 is administered to a delivery region of a cellular organism in the form of a patient treatment site 112. This is effected by the use of a substance delivery device which in this example is also a handheld device in the form of an aerosol delivery gun 110.

In this example, the patient treatment site 112 is a specific region of the skin of a patient which requires administration of an aerosol form of a drug. However, the patient treatment site could be for example a patient's cornea. The patient treatment site can also include an opening to a patient's lungs involving their mouth and/or nose or more specifically a membrane of the patients lungs. The aerosol delivery gun 110 includes radiation or energy generating means for enhancing delivery of aerosol 26 to the patient treatment site 112. In this particular example the radiation or energy generating means is a magnetic field generator which includes a magnetic inductor 116 and a corresponding electronic generator 118. The aerosol delivery gun 110 also includes an aerosol delivery head which in this example comprises aerosol delivery compartment 114 for provision of aerosol 26 to the patient treatment site 112.

The aerosol delivery compartment 114 includes walls 120 which extend away from the magnetic inductor 116 in a divergent manner. A compartment outlet in the form of aerosol outlet 125 is formed between ends 122 of the delivery compartment walls 120 which are designed for application against the patient treatment site 112 to create a substantially sealed compartment 124. If the patient treatment site is a patient's cornea, the aerosol delivery compartment is designed so that ends 122 of its walls 120 contact skin covering the patient's eye socket to form a substantially sealed compartment covering the cornea. The substantially sealed compartment 124 enables aerosol 26 to be contained between the patient treatment site 112 and the magnetic inductor 116, and evenly dispersed over the patient treatment site 112. The aerosol 26 can be supplied to the aerosol compartment 114 via a closed compartment, for example, closed compartment 126 or alternatively, can be supplied directly from a nebulizer, for example, ultrasonic nebulizer 30, 54 or 80 via an inlet in the form of inlet pipe 125.

With aerosol 26 contained within the aerosol delivery compartment 114 as shown in figure 5 passive transdermal aerosol delivery to the patient via the patient treatment site 112 is more effective than it would be if the aerosol was otherwise delivered. The aerosol delivery compartment 114 of the aerosol delivery gun 110 therefore enhances transdermal drug delivery by concentrating aerosol 26 near the patient treatment site 112 and evenly distributing it over that site. The aerosol delivery gun 110 further enhances transdermal delivery of aerosol 26 which condenses on the patient treatment site 112 by applying a magnetic field, via the magnetic inductor 116, to the patient treatment site 112. The general direction of propagation of the magnetic field is represented by arrow 128. The magnetic field facilitates the active transdermal transport technique known as magnetophoresis.

The aerosol delivery gun 110 is effective for delivery of a substance to sensitive patient treatment areas, for example, a patient's cornea. It enables the substance to be applied to the cornea without the cornea being contacted by anything other than the aerosol 26. This is possible because the magnetic field generator of the aerosol delivery gun 110 does not contact the patient treatment site. The aerosol delivery gun 110 is also effective for delivery of a substance to a patient's lungs.

By ionising the aerosol 26 it can be more efficiently and effectively delivered to the patient treatment site 112. The ionised aerosol 26 is attracted to the patient treatment site 112 by oppositely charging the patient treatment site 112. The aerosol 26 can be charged before or after its entry into the aerosol delivery compartment 114.

Figure 6 schematically depicts another example of a handheld device in the form of a substance delivery gun 132 which is suitable for delivering a substance, for example, in aerosol, liquid or gel form, to a delivery region of a cellular organism which in this example is patient treatment site 134. The patient treatment site 134 is identical to the patient treatment site 112 described above in relation to the aerosol delivery gun 110. The substance delivery gun 132 houses radiation or energy generating means for generation of three different forms of radiation or energy which in this example include sonic or ultrasonic, electric and magnetic radiation. The substance delivery gun 132 also includes a radiation delivery head which can take the form of a radiation delivery compartment 135 (see figure 5) which is identical to the aerosol delivery compartment 114 of the aerosol delivery gun 110. Alternatively, the radiation delivery head can take the form of a radiation delivery plate 141 (see figure 6). The radiation delivery compartment and plate

135 and 141 also function as and are examples of substance delivery components in the form of substance delivery compartment 137 (see figure 5) and substance delivery plate 145 (see figure 6). The substance delivery compartment 137 can be used for delivery of aerosol to the patient treatment site 134 as explained above in relation to the aerosol delivery gun 110. The substance delivery compartment 137 can also be used for delivery of, for example, a liquid or gel form of a substance to the patient treatment site 134. However, when the substance delivery compartment 137 is used for aerosol delivery, the corresponding radiation or energy generating means generating sonic or low frequency ultrasonic radiation either alone or in combination with electric and/or magnetic radiation. High frequency ultrasonic radiation is not used for aerosol delivery because it requires a liquid or gel medium for effective transmission. The substance delivery plate 145 is suitable for delivery of a gel form of a substance to the patient treatment site 134.

By providing a substance at the patient treatment site 134, via the substance delivery compartment 137 or substance delivery plate 145 the substance delivery gun 132 aids passive transdermal drug delivery for reasons described above in relation to the aerosol delivery gun 110. The substance delivery gun 132 further enhances transdermal substance delivery by simultaneously applying ultrasonic, electric and magnetic fields to the patient treatment site 134 which, in the case of substance delivery compartment 137, aerosol 26 is contained at the patient treatment site 134, and in the case of the substance delivery plate 145, a gel form of a substance is located at the patient treatment site 134. The ultrasonic, electric and magnetic radiation applies to the substance respective active transdermal transport techniques of sonophoresis, iontophoresis and electroporation, and magnetophoresis.

Referring to figure 6, the substance delivery gun 132 includes an ultrasonic field generator which in this example consists of an electro acoustic transducer 136 and an electronic generator 144. The electronic generator 144 supplies power to the electro acoustic transducer 136. The electro acoustic transducer is formed of a piezoceramic 138 which is covered on opposite sides by metal electrodes 140 and 142. The electro acoustic transducer 136 is formed of diamagnetic material which is transparent to magnetic fields generated by the magnetic field generator.

The electro acoustic transducer 136 is designed to operate at two frequencies. At a low to mid frequency the transducer induces transdermal cavitation, a mechanism of

sonophoresis. At a second significantly higher frequency the electro acoustic transducer 136 does not induce cavitation and is used in combination with the low to mid frequency ultrasonic radiation to avoid tissue damage which is known to occur with low to mid frequency ultrasonic radiation when it is applied at high power.

The electric field generator of the substance delivery gun 132 is in the form of a direct current electric circuit 146 which connects the patient treatment site 134 to the metal electrode 142 via electrode 143. The direct current electric circuit 146 includes an electric current generator 148.

The magnetic field generator of the substance delivery gun 132 is in this particular example a magnetic inductor 150 which is supplied electric current by an electronic generator 152. The electronic generator 152 is designed to produce different forms of voltage to create different types of magnetic fields including asymmetric pulse magnetic fields.

The general direction of propagation of the ultrasonic, electric and magnetic fields is represented by arrow 160. The radiation field generators of the substance delivery gun 132 are designed to simultaneously generate each of the three different forms of radiation fields. The fields are one example of how ultrasonic, electric and magnetic fields can be combined in a synergistic manner whereby the three different forms of radiation fields collectively enhance delivery more than the sum of delivery enhancements achievable through independent application of the three different forms of radiation fields.

Fluorescence confocal images 210, 212 and 214 of the figures 7, 8 and 9 respectively demonstrate the effectiveness of the substance delivery gun 132. The fluorescence confocal images 210, 212 and 214 are images of three different layers of a subject's skin following transdermal delivery of a fluorescent dye through the skin using the substance delivery gun 132. The fluorescent dye was delivered to the subject over a six minute period of time using the substance delivery gun 132 having radiation or energy generating means for simultaneous generation of ultrasonic, electric and magnetic radiation fields defined by the following respective parameters: 0.88 MHz at $1W/cm^2$ intensity and a 50% duty cycle of 10ms; 1mA; and 20mT.

Image 210 is an image of a stratum corneum layer, image 212 is an image of a deeper stratum spinosum layer and image 214 is an image of a third layer which is slightly

deeper than that corresponding to image 212. Bright regions of images 210, 212 and 214 represented by reference numerals 216, 218 and 220 respectively indicate the presence of fluorescent dye.

Referring to figure 7, the bright regions 216 correspond to intercellular space between corneocyte cells of the stratum corneum. The bright regions 216 therefore indicate the presence of fluorescent dye in the intercellular spaces of the stratum corneum.

The stratum spinosum skin layer of image 212 is formed mainly of keratinocyte cells with the remainder of this layer being formed of a fibrous arrangement of cells known as the dermal papillae which protrude into the stratum spinosum layer from a slightly deeper region of the skin. The bright coloured regions 222 are unclear in the image 212 however in the corresponding original image bright coloured regions 222 form a honeycomb structure. Bright regions 222 indicate the presence of fluorescent dye in intercellular space between keratinocyte cells. Bright region 224 is also unclear although the corresponding original image gives the appearance of a dark annular region having light distributed throughout. Bright regions 224 indicate the presence of fluorescent dye throughout the dermal papillae.

Image 214 of figure 9 corresponds to a skin layer formed predominantly of dermal papillae. Visible in image 214 is a fluorescent dye stained dermal papillae 226 and the edge of another fluorescent dye stained dermal papillae 228.

Transdermal delivery of a fluorescent dye using a substance delivery gun 132 resulted in the delivery of fluorescent dye to each of the layers represented by the images of figures 7, 8 and 9. Passive delivery of a fluorescent dye to the subject results in a similar concentration of dye to that represented by image 210 reaching the stratum corneum layer over a six minute time period. However, regardless of the elapsed time, fluorescent dye does not reach skin layers corresponding to images 212 or 214 via passive diffusion techniques.

A substance delivery gun 170 which is schematically represented by figure 10 is a modified version of the substance delivery gun 132. For ease of reference like features of the substance delivery guns 132 and 170 are referred to by common reference numerals. The substance delivery gun 170 includes an energy concentrator 172. An electro acoustic transducer 174 having a piezoceramic (not shown) is positioned at an end of the energy

concentrator 172 which is remote from a patient treatment site 178. A direct current electric circuit 180 connects the patient treatment site 178 to the energy concentrator 172. The direct current electric circuit 180 includes an electric current generator 148 referred to above in relation to the substance delivery gun 132. In place of the magnetic inductor 150 of the substance delivery gun 132, the substance delivery gun 170 includes a magnetic inductor 182 which is mounted to a tapered end 184 of the energy concentrator 172 which is adjacent the patient treatment site 178. The magnetic inductor 182 is connected to an electronic generator 152 referred to in relation to the substance delivery gun 132. The energy concentrator 172 is constructed from a metal having ferromagnetic properties which enable magnetic and acoustic fields of the substance delivery gun 170 to be enhanced.

The substance delivery gun 170 otherwise corresponds to the substance delivery gun 132 and includes features described above in relation to the substance delivery gun 132. The substance delivery gun 170 however has, by virtue of the energy concentrator 172 enhanced substance delivery capability to that of the substance delivery gun 132.

Referring to figure 11, another alternative form of the substance delivery gun 132 of figure 6 is substance delivery gun 186. Details of the substance delivery gun 186 are explained by reference to substance delivery guns 132 and 170 of figures 5 and 6 respectively. Like features of substance delivery guns 132, 170 and 186 are referred to by common reference numerals. The substance delivery gun 186 includes an electro acoustic transducer 188 consisting of a piezoceramic 190 and metal electrodes 192 and 194 which sandwich the piezoceramic 190 there between, a magnetic inductor 182 and a corresponding electronic generator 152 referred to above in relation to the substance delivery gun 132, and a direct current electric circuit 200. The electro acoustic transducer 188 is similar to the electro acoustic transducer 136 except that it includes apertures 196 for passage there through of electroporation electrodes 198. The direct current electric circuit 200 is identical to the direct current electric circuit 180 of the substance delivery gun 170 except that it connects to a circuit which connects the electronic generator 144 with the metal electrodes 192 and 194 of the electro acoustic transducer 188, rather than connecting to an energy concentrator. The magnetic radiation generating means of the substance delivery gun 186 includes a magnetic inductor 182 which is as described above in relation to the magnetic inductor 182 of the substance delivery gun 170 except that it encircles electroporation electrodes 198 rather than a tapered end of an energy concentrator.

The electrodes 198 form part of a second electric generator which in this example enables electroporation to be applied to a substance for its delivery to a patient treatment site 200. The second electric generator, in this particular example, also includes an electric generator 202 which generates electricity for the electroporation electrodes 198. The electroporation electrodes 198 are made of a ferromagnetic material which helps to concentrate and transport magnetic radiation to the patient treatment site 200.

The substance delivery gun 186 also includes a substance storage compartment 204 for storage of a unit dose of a substance for delivery to the patient treatment site 200. During delivery of the substance to the patient treatment site 200, the substance functions as a transmission medium for ultrasonic energy emitted by the electro acoustic transducer 188.

Now that various examples of a preferred embodiment and method of delivering a substance into a cellular organism have been described, it will be apparent to those skilled in the art that the preferred embodiment and methodology have at least the following advantages:

(a) the efficiency and effectiveness of the nebulizer is maintained during nebulization unlike the prior art where the liquid level is progressively lowered with conversion of the liquid into aerosol;

(b) the device effectively provides an aerosol form of a substance at a delivery region of a cellular organism for delivery thereto;

(c) the application of an aerosol form of a substance to delivery regions of a cellular organism is possible where contact of the delivery regions by liquid or solid matter is adverse or sensitive;

(d) the delivery of an aerosol form of a substance into a cellular organism is possible through active transport techniques involving the application of one or more forms of radiation or energy;

(e) the delivery of an aerosol form of a substance into a cellular organism is possible through simultaneous application of two or more different forms of radiation or energy;

(f) the delivery of an aerosol form of a substance into a cellular organism is possible through simultaneous application of two or more different forms of radiation or energy in a synergistic manner whereby different form of radiation or energy collectively enhance delivery more than the sum of

delivery enhancements achievable through independent application of the different forms of radiation or energy;

(g) the substance delivery can be confined to a relatively small part of a cellular organism by simultaneous application of two or more different forms of radiation via a radiation delivery head of a substance delivery gun; and

(h) the delivery of a substance via a delivery gun through simultaneous application of two or more different forms of radiation or energy in a synergistic manner whereby different forms of radiation or energy collectively enhance delivery more than the sum of delivery enhancements achievable through independent application of the different forms of radiation or energy.

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. For example, the specific shape and design of the nebulizer, and the aerosol and substance delivery guns, as well as the specific shape, design or configuration of components or assemblies that they comprise may vary provided they function as broadly defined.

All such variations and modifications are to be considered within the scope of the present invention the nature of which is to be determined from the foregoing description.

It is to be understood that a reference herein to a prior art document does not constitute an admission that the document forms part of the common general knowledge in the art in Australia or in any other country.

The claims defining the invention are as follows:

1. A method of delivering a substance into a cellular organism, the method comprising the steps of:

providing the substance in an ionised aerosol form at a delivery region of the organism; and

applying magnetic energy to the delivery region to effect enhanced delivery of the ionised aerosol substance to the cellular organism.

2. A method as defined in claim 1 wherein the application of magnetic energy is effected by applying a pulsed magnetic field.

3. A method as defined in claim 2 wherein the pulsed magnetic field is asymmetric.

4. A method of delivering a substance into a cellular organism, the method comprising the steps of:

providing the substance in a liquid or cream form at a delivery region of the organism;

applying ultrasonic energy to the delivery region to enhance delivery of the cream or liquid substance to said organism; and

simultaneously applying magnetic energy and electrical energy to the delivery region to effect delivery of the cream or liquid substance to the cellular organism.

5. A method as defined in claim 4 wherein the application of ultrasonic energy to said organism to enhance delivery is promoted by opening of pores of the organism.

6. A method as defined in any one of the preceding claims wherein the ultrasonic and magnetic energies are applied simultaneously.

7. A method as defined in any one of the preceding claims wherein the application of ultrasonic, magnetic and/or electrical energy is effected by applying ultrasonic, magnetic and/or electrical fields, respectively.

8. A method as defined in claim 7 wherein the magnetic field is a pulsed magnetic field.

9. A device for delivering a substance into a cellular organism, the device comprising:

an aerosol delivery head for providing the substance in an ionised aerosol form at a delivery region of the organism;

means for applying magnetic energy to the delivery region to effect enhanced delivery of the ionised aerosol substance to the cellular organism.

10. A device as defined in claim 9 wherein the aerosol delivery head provides a sealed compartment about the delivery region.

11. A device as defined in either of claims 9 or 10 also comprising a nebulizer being operatively coupled to the aerosol delivery head.

12. A device as defined in Claim 11 wherein the nebulizer includes:

a container being adapted to contain a liquid to be nebulized.

a tubular energy transmitter having one end immersed in the liquid of the container and an opposite end positioned clear of the liquid; and

an energy source being operatively coupled to the container or the tubular energy transmitter for nebulization of the liquid and being arranged for transmission of energy to the liquid or tubular energy transmitter whereby in operation the transmitted energy forces the liquid toward the opposite end of the tubular energy transmitter where it is nebulized in the form of the aerosol.

13. A device as defined in claim 12 wherein the energy transmitter is positioned so that said one end is adjacent the bottom of the liquid.

14. A device as defined in either of claims 12 or 13 wherein the energy transmitter is arranged to allow formation of high frequency vibrations in its wall(s) upon emission of the energy, the high frequency vibrations effecting aerosol formation at the liquid surface at or adjacent the opposite end of the energy transmitter.

15. A device as defined in any one of Claims 12 to 14 wherein the nebulizer also includes an aerosol tube coupled to the opposite end of the tubular energy transmitter and having a cross-sectional area such that the static pressure of the aerosol within the aerosol tube induces a pressure drop along the aerosol tube which alone is sufficient to propel the nebulised aerosol through the aerosol tube.

16. A device for delivering a substance into a cellular organism, the device comprising:

means for generating ultrasonic energy being adapted to cooperate with a delivery region of the organism to enhance delivery of the substance in a cream or liquid form to said organism;

means for simultaneously applying magnetic energy and electrical energy to the delivery region to effect delivery of the cream or liquid substance to the cellular organism, said ultrasonic generating means being operatively coupled to the magnetic and electrical energy means whereby a synergistic effect is provided by the combination of said means.

17. A device as defined in claim 16 wherein the means for applying magnetic energy is in the form of a pulsed magnetic generator.